Economic evaluation of extended and conventional prophylaxis with enoxaparin against venous thromboembolism in patients undergoing surgery for abdominal cancer

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three prophylactic strategies against venous thromboembolism (VTE) were examined in patients undergoing surgery for abdominal cancer. The three strategies were:

- conventional unfractionated heparin (UFH) prophylaxis, with 5,000 IU UFH taken three times a day for 8 days (CUP);
- conventional enoxaparin prophylaxis, with 40 mg enoxaparin taken once daily for 8 days (CEP); and
- extended enoxaparin prophylaxis, with 40 mg enoxaparin taken once daily for 8 days in hospital followed by a further 21 days’ prophylaxis in an outpatient setting (EEP).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients aged 40 years or older who were undergoing curative surgery for abdominal cancer. The operation was expected to last at least 45 minutes and the patients had a life expectancy of at least 6 months.

Setting
The setting was secondary care. The economic study was conducted in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1994 and 2002. No dates for the resource use data were reported. The costs were presented in 2001/2002 values.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.

Modelling
A decision tree model was used to assess the costs and benefits of the three alternative prophylactic strategies in a hypothetical cohort of 100 patients. Similar branches of the tree were reported for all three interventions, as shown in the tree represented in the paper. Patients receiving prophylactic therapies could develop or not develop deep vein
thrombosis (DVT). DVT could become symptomatic or not, and progress to pulmonary embolism (PE) and then to death. All the patients were followed until they died. The model appears to have been deterministic.

**Outcomes assessed in the review**
The outcomes assessed included the probability values of:

- objectively diagnosed DVT becoming symptomatic;
- PE becoming symptomatic;
- "false positive" DVT symptoms;
- "false positive" PE symptoms;
- untreated DVT leading to PE;
- surviving 1 hour post PE;
- surviving untreated PE given survival at 1 hour;
- surviving treated PE given survival at 1 hour;
- surviving untreated DVT (no PE).

Also assessed were the following efficacy or safety rates:

- the rate of objectively diagnosed DVT following prophylaxis with EEP, CEP or CUP;
- the rate of major bleeding following prophylaxis with EEP, CEP or CUP;
- the percentage of patients able to self-administer; and
- life expectancy.

**Study designs and other criteria for inclusion in the review**
A systematic review of the literature was not undertaken. The evidence came from randomised trials and a systematic review.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
The validity of the primary studies was not explicitly discussed. However, some of the evidence came from randomised trials and a systematic review, which have implicitly a high internal validity.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Four primary studies were included in the review.
Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability values were:

0.162 for objectively diagnosed DVT becoming symptomatic;
0.290 for PE becoming symptomatic;
0.1 for “false positive” DVT symptoms;
0.020 for “false positive” PE symptoms;
0.115 for untreated DVT leading to PE;
0.890 for surviving 1 hour post PE;
0.7 for surviving untreated PE given survival at 1 hour;
0.920 for surviving treated PE given survival at 1 hour; and
0.994 for surviving untreated DVT (no PE).

The efficacy and safety rates were as follows:

the rate of objectively diagnosed DVT was 0.048 following prophylaxis with EEP, 0.120 with CEP and 0.149 with CUP;
the rates of major bleeding were 0.040 for prophylaxis with EEP, 0.040 with CEP and 0.028 with CUP;
the percentage of patients able to self-administer was 0.598; and
life expectancy was 3 years.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of VTE-related events. This included diagnosed DVT, diagnosed PE and episodes of major bleeding. However, the number of life-years lost with each strategy was also reported and combined with the costs. The mortality rates were calculated by multiplying the estimated frequency of PE events by the proportion of fatal PE (derived from the literature).

Direct costs
Discounting was not relevant since the time horizon of the study was short, owing to the poor survival of the patients considered in the analysis. The unit costs and the quantities of resources used were presented separately. The health services included in the economic evaluation were drugs and consumables, procedures, and hospital and staff services. Drugs and consumables covered enoxaparin, UFH, low molecular weight heparin (LMWH), warfarin, compression stockings, syringes and needles. The procedures included ultrasound, perfusion/ventilation scan, chest X-ray, electrocardiogram, angiograms, blood/platelet count and prothrombin/thrombin test. Hospital and staff services covered...
intensive care unit stay, hotel stay, physician and nurse time, and the district nurse. The cost/resource boundary of the NHS was adopted. The resource use data were mainly derived from authors' assumptions on treatment patterns. The costs came from the British National Formulary, NHS Reference Costs, PSSRU, and published studies. The costs were presented in 2001/2002 values and were inflated, if necessary, using the Hospital and Community Health Services inflation indices.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical tests were conducted.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
Univariate sensitivity analyses were conducted to determine whether the estimated cost-effectiveness ratios were robust to variations in the model inputs. The model inputs investigated were the risk of VTE, rate of self-injection, drug and hospital costs, UFH regimen, drug efficacy and the percentage of patients undergoing chemotherapy. The ranges used were plausible, but the sources of these ranges were not reported. Some values (i.e. drug efficacy) were varied within the confidence interval.

**Estimated benefits used in the economic analysis**
The estimated number of VTE-related events in the cohort of 100 patients was 5.8 with CUP (2.6 diagnosed DVT, 0.4 diagnosed PE and 2.8 episodes of major bleeding), 6.5 with CEP (2.1, 0.3 and 4.0, respectively), and 4.9 with EEP (0.8, 0.1 and 4.0, respectively). The life-years lost were 2.5 with CUP, 2 with CEP and 0.8 with EEP.

**Cost results**
The estimated costs in the cohort of 100 patients were £20,200 with CUP, £18,600 with CEP and £46,200 with EEP. The higher cost of EEP was due to the higher cost of prophylaxis relative to CUP and CEP. The cost associated with VTE or major bleeding was lower for EEP.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the prophylactic strategies.

The incremental analysis showed that CEP and CUP had a similar effectiveness (no statistically significant difference between the number of VTE-related events). However, CEP was consistently less costly than CUP, which was dominated.

The incremental cost per life-year gained was £15,300 with EEP over CUP, and £22,700 with EEP over CEP.

The base-case results were generally robust to variations in the model inputs.

Although the authors stated that the cost-effectiveness of EEP was sensitive to variations in the baseline risk of VTE, the cost of enoxaparin and the efficacy of CUP and EEP, it appears that the only parameter with a strong influence in the final ratios was the efficacy of EEP.
Authors' conclusions
Compared with unfractionated heparin (UFH), conventional enoxaparin prophylaxis (CEP) was a cost-effective intervention in patients undergoing curative surgery for abdominal cancer. An intense protocol based on extended enoxaparin prophylaxis (EEP) was more effective, but it increased costs from the perspective of the National Health Service (NHS).

CRD COMMENTARY - Selection of comparators
The authors discussed the reasons for their choice of the comparators. They stated that prophylaxis with UFH or LMWH was a standard treatment for patients at risk of VTE. However, the optimal treatment strategy was unclear. Therefore, the choice of UFH (standard treatment) and two alternative treatments based on different dosages of enoxaparin appears to have been appropriate. However, other LMWH-based treatment may have been available. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies but a systematic review of the literature was not undertaken. In fact, the studies appear to have been identified selectively. The design of some studies was reported, but there was no detailed information on the study sample and interventions. Thus, it is difficult to assess the internal validity of the sources used. Further, the methods used to extract and combine the primary estimates were not reported. To deal with the issue of uncertainty in the primary estimates, the model inputs were varied in the sensitivity analysis. This enhances the validity of the analysis.

Validity of estimate of measure of benefit
The main summary benefit measure (life-years gained) was appropriate as it represented a key aspect of the impact of the intervention on patient health. Since the expected survival of this patient population was poor, no discounting was required. The use of survival allows comparisons to be drawn with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. Detailed information on the quantities of resources used, unit costs, price year and source of the costs was provided. A breakdown of the cost items was also reported. This enhances the possibility of performing reflation exercises and of replicating the study in other settings. The costs were treated deterministically in the base-case but some cost inputs were varied in the sensitivity analysis. However, the source of the resource use data was unclear. The authors noted that hospitals could achieve discounts from list prices, which were the source of the enoxaparin costs. Thus, the cost-effectiveness of CEP improved. This had little impact on the cost-effectiveness of EEP as nurse time, rather than drug use, was the cost driver for EEP.

Other issues
The authors did not make extensive comparisons of their results with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Some sensitivity analyses were conducted, but the overall external validity of the analysis was low. The study referred to patients undergoing surgery for abdominal cancer and who were at risk of VTE, and this was reflected in the conclusions of the study. Finally, the authors underlined the fact that EEP might be particularly attractive in high-risk patients, given the reduction in VTE-related events.

Implications of the study
The authors suggested that further research should corroborate the results of the current study using a cost-utility approach. In addition, it should validate some of the key model inputs, such as the rate of symptomatic VTE. The adoption of a wider perspective, including patient and carer costs, would be interesting.
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Bibliographic details

Other publications of related interest


Indexing Status
Subject indexing assigned by CRD

MeSH
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